# Polycythemia Vera

## Peripheral Vascular Manifestations

WESLEY S. MOORE, *M.D.*, F. WILLIAM BLAISDELL, *M.D.*, and ALBERT D. HALL, *M.D.*, San Francisco

• **The presenting manifestations of polycythemia vera are often complications involving the vascular system. These include myocardial infarction, cerebro-vascular accidents and ischemic changes in the extremities.**

**The concept of increased atherogenesis in cases of polycythemia vera has been questioned. A possible mechanism by which small, otherwise subclinical atheromatous plaques produce ischemic symptoms in patients with polycythemia vera is discussed. The blood in polycythemic patients has been shown to have an increased viscosity resulting in a prolonged circulation time. If a small atheromatous plaque is present in association with increased blood viscosity, this combination may well produce ischemic symptoms. This explains why treatment of polycythemia vera, with restoration of blood to normal viscosity, often reverses the patient's ischemic symptoms.**

**Two cases of polycythemia vera here reported, in which the presenting manifestations were gangrenous extremities, emphasize the need for prompt diagnosis and treatment of polycythemia vera. In the first case, early recognition and treatment of polycythemia vera successfully reversed the ischemic changes in the extremities, while failure of early recognition and treatment in the second case resulted in two major amputations.**

WITH THE ADVANCE of vascular reconstructive techniques, interest in the arterial occlusive diseases has been renewed. Arteriosclerosis is by far the most common cause of vascular obstruction, although tissue overgrowth, inflammation, embolism or thrombosis also may result in vascular insufficiency. This report is concerned with one of the rarer causes of peripheral vascular insufficiency—polycythemia vera. The two cases herein described were of interest because the initial manifestations were gangrenous changes in the lower extremities. Earlier recognition of polycythemia might have prevented the thrombotic complications which in one case led to the loss of a limb.

CASE 1. A 70-year-old white man was admitted to Veterans Administration Hospital, San Francisco, in November, 1956, with severe rest pain and blue discoloration in the right great toe. A portion of the tip of the toe near the nail had sloughed off from progressive gangrene. On physical examination, the femoral, popliteal, dorsalis pedis and posterior tibial pulses were full and equal. Hemoglobin content was 20.5 gm per 100 ml of blood, the packed cell volume was 64 per cent. Erythrocytes numbered 7,500,000 per cu mm and the platelet count was 336,000 per cu mm. Bone marrow aspiration revealed both erythroid and myeloid hyperplasia consistent with polycythemia vera. Multiple phlebotomy and treatment with $P_{32}$ were carried out and the hemoglobin level was reduced to a normal range. The toes healed without further incident and the patient was asymtomatic at the time of discharge. He was treated for polycythemia at varying intervals with no further peripheral vascular symptoms until April, 1961, when he was readmitted with a three-month history of aching pain and bluish discoloration of the left second toe. Shortly thereafter he noted pain and bluish discoloration of the left great toe.

On physical examination, the left great toe was purple and cold with poor capillary filling. The remainder of the foot was warm and healthy in appearance. The right foot was cooler than the left. In the interval since the previous admission, the popliteal, dorsalis pedis, posterior tibial pulses on the right side as well as the dorsalis pedis pulse on the left had disappeared. Paradoxically, the patient kept his leg elevated rather than dependent in order to relieve the pain.

Erythrocytes numbered 8,810,000 per cu mm, packed cell volume was 68 per cent, hemoglobin content was 19.4 gm per 100 ml and the platelet count 443,000 per cu mm. A blood volume determination was 110 ml per kilogram of body weight (normal value 65.5 ml per kilogram); the red cell mass was 73.2 ml per kilogram (normal value 30.7 ml per kilogram). On arteriography the aorta, iliac and common femoral vessels appeared normal. The right superficial femoral artery was occluded. The left superficial femoral and both popliteal arteries and their major branches were patent but had ragged, irregular contours compatible with diffuse arteriosclerotic involvement. The patient was treated with

From Surgical Service, Veterans Administration Hospital, San Francisco, and University of California School of Medicine, San Francisco.
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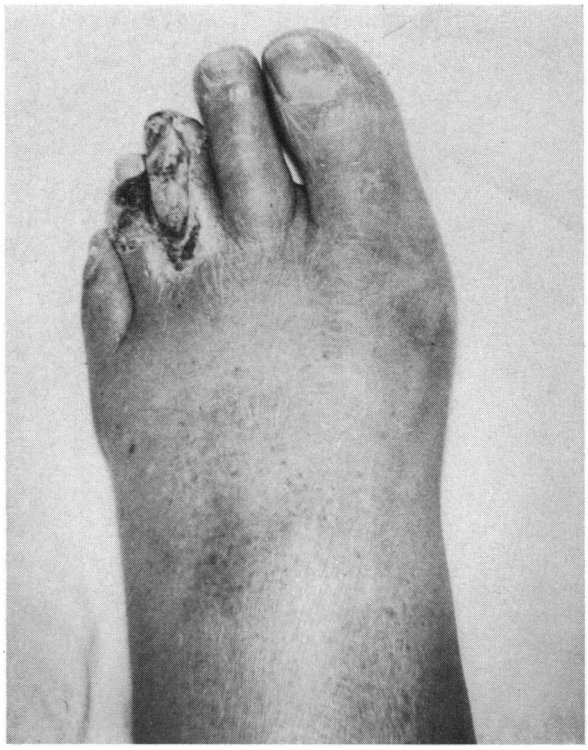

Figure 1.—(Case 2). Gangrenous changes in the third and fourth toes of left foot.

phlebotomy, $P_{32}$ and bilateral lumbar sympathectomy. He gradually became asymptomatic and was discharged, hemoglobin content at that time being 12 gm per 100 ml, and packed cell volume 43 per cent.

CASE 2. A 71-year-old white man was admitted to Veterans Administration Hospital, San Francisco, in November 1961 with chief complaint of gangrenous changes of the left third toe. Five months earlier he had been admitted to another hospital because of reactivation of a peptic ulcer, with pain and bleeding. This improved on medical treatment. During that period in hospital he noted pain and coldness in the toes of both feet, which progressed to gangrene of the three toes on the right despite lumbar sympathectomy. Right transmetatarsal amputation was unsuccessful and this was followed by a below-the-knee amputation. Because of similar but milder conditions in the left foot, left lumbar sympathectomy was also carried out. The patient was then discharged and did well until three weeks before the present admission, when he developed pain in the left third toe.

On examination a draining sinus in the right below-the-knee amputation stump was noted. The left third and fourth toes were gangrenous and pronounced rubor was observed in the distal foot when it was dependent (Figure 1). Both femoral and popliteal pulses were full. The left posterior tibial pulse was present; the dorsalis pedis pulse absent.

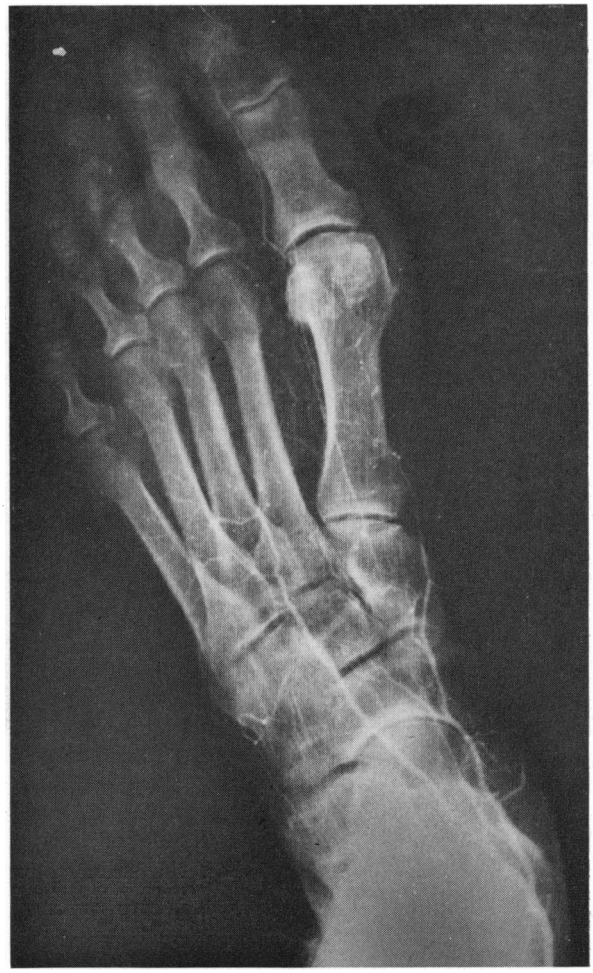

Figure 2.—(Case 2). Arteriogram demonstrating open posterior tibial artery but absence of the dorsalis pedis artery and plantar arch.

Hemoglobin content was 15.3 gm per 100 ml of blood. Results of blood sugar studies were within normal limits. Serum examinations for macroglobulins and cryoglobulins were negative. A platelet count was 826,000 per cu mm and when repeated was 1,360,000. Wintrobe indices revealed microcytic hypochromic anemia. Bone marrow studies showed hyperplasia of the erythroid and megakaryocytic elements. Iron-staining of bone marrow revealed iron deficiency anemia. A diagnosis of polycythemia vera, masked by iron deficiency anemia, was made. Aortography and left femoral arteriography revealed no significant vascular occlusive disease in these larger vessels. Peripheral arteriograms demonstrated obliteration of the plantar arch and absence of the dorsalis pedis artery shadows (Figure 2). Transmetatarsal amputation was done and the stump healed without incident. Pathologic sections showed intimal proliferation and thrombosis of distal small vessels (Figure 3).

Iron therapy was given and the number of ery-

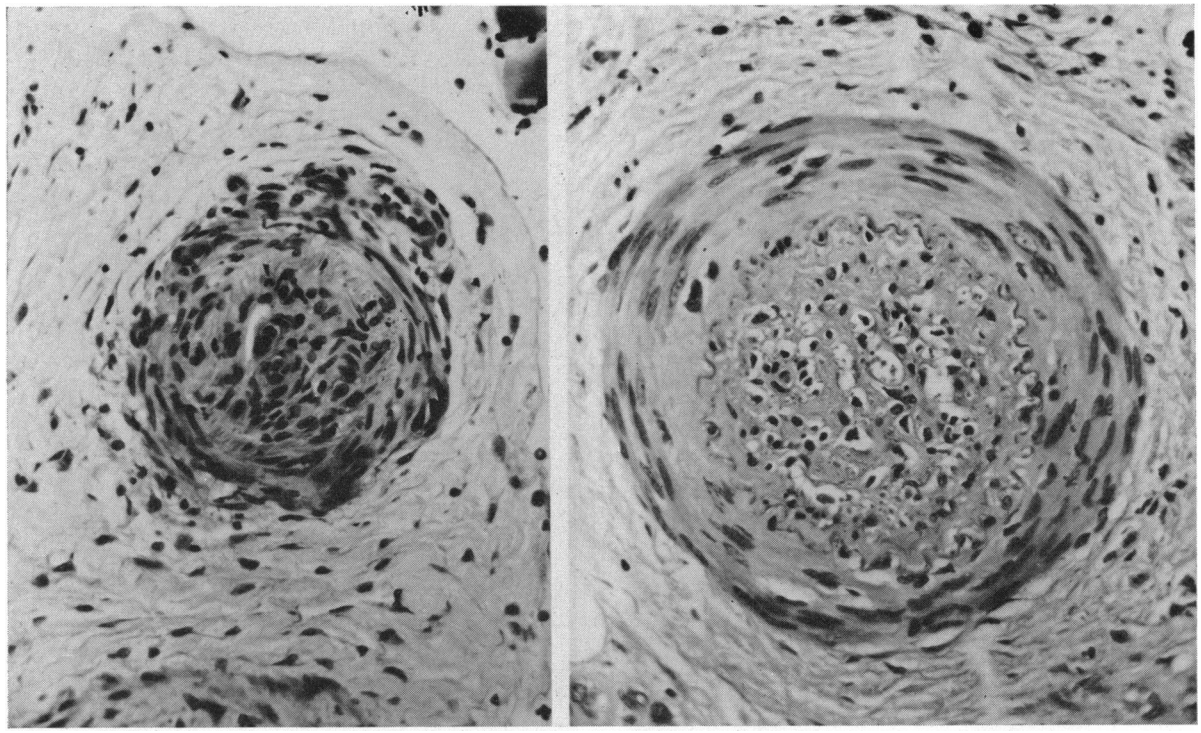

Figure 3.—(Case 2). Hematoxylin and eosin stained sections of amputation specimen from left foot. Arterioles with organized thrombi within the lumina (× 130).

throcytes and the hemoglobin content increased promptly. Treatment with $P_{32}$ thereupon was begun and at the time of discharge the hematologic findings were within normal limits. Since that time the patient has been carefully observed, and the typical course of polycythemia has been noted and appropriate therapy reapplied at varying intervals. There were no further manifestations of peripheral vascular disease.

#### HISTORICAL FEATURES

Polycythemia vera is a disease of unknown cause, characterized by a persistent elevation in the total number of red cells in circulation, splenomegaly, leukocytosis and thrombocytosis. It was first described by Vaquez in 1892.[10] Osler, in 1903, elaborated upon the phenomenon in the English literature and first recognized the frequency of associated vascular complications.[8] Brown and Giffin in 1926 were the first to recognize that most of the symptoms in polycythemia vera are on a circulatory basis.[2] In a later article they also noted that the most common complications in polycythemia vera were those involving the vascular system.[3]

The vascular manifestations may roughly be divided into three major categories: Thrombosis, hemorrhage and pain from capillary distention. Oppenheimer in 1929 presented seven cases involving vascular disturbances in association with polycythemia vera; these included one case of coronary thrombosis, one case of hepatic vein thrombosis, one case of occlusive disease involving an extremity, two cases of pain secondary to capillary distention and two of cerebral thrombosis.[7]

Brown and Giffin, reviewing 100 cases of polycythemia vera in the Mayo Clinic series from 1912-1929, reported on 27 cases involving vascular complaints in the extremities.[3] These were divided into three categories: the first consisted of 20 cases with associated arteriosclerosis obliterans; this included six cases of claudication, one case of acute thrombotic occlusion leading to gangrene, and 13 cases of acroparesthesias. The second group consisted of one case presenting the picture of thromboangiitis obliterans, and the third, a group with vasomotor disturbances, including three cases of erythromelalgia and three cases of Raynaud's phenomenon. These investigators felt that there was a definite increased incidence of arteriosclerosis obliterans in a group with polycythemia vera as opposed to a similar cross-section of population in the same age and sex distribution. Norman and Allen reviewed 98 cases of polycythemia vera in the Mayo Clinic series from 1929 to 1936. They found that in 33 cases (or 34 per cent) there were vascular complications.[6] This is a much higher incidence than occurs in the general population, and the investigators felt that it represents a causal relationship rather than co-

incidence. Burris and Arrowsmith in 1953, reporting on the Tulane series, noted that 23 of a total of 68 patients (or 33.8 per cent) had vascular complications.[4] Bluefarb in 1955 stated that arteriosclerosis obliterans was more common in patients with polycythemia than in others in a comparable age group.[1]

The factors productive of vascular complications in polycythemia vera are not fully understood, but several mechanisms have been suggested. Brown and Giffin in 1930 pointed out that the rate of circulation as measured by the histamine time was 5 to 10 times slower in polycythemia vera than in normal subjects. They felt that sluggish circulation, high viscosity, increase in platelets and hypercalcemia predisposed to thrombosis and accelerated the rate of peripheral arteriosclerosis obliterans.[3]

Damashek demonstrated that the greater the hematocrit level, the more viscid the blood and the slower the velocity of blood flow.[5] Rosenthal considered it curious that both thrombosis and hemorrhage were concurrent complications in polycythemia vera. He pointed out that in spite of thrombocytosis, clot retraction may be slow, little serum may be formed and that perhaps this results from the increase in blood cell mass. He felt that these features not only explain the abnormal tendency to thrombosis, but that the blood vessel engorgement and poor clot retraction ability provide an explanation for frequent hemorrhage.[10] Wilson, Heath and Larsen studied the coagulation abnormalities in polycythemia vera.[11] They also pointed out the paradox of thrombosis and hemorrhage as concomitant complications in polycythemia vera. They concurred with the postulate that increased red cell mass, elevated hematocrit, thrombocytosis and high viscosity were the responsible factors in thrombotic phenomena. They did not believe that a decrease in prothrombin and fibrinogen levels produced the hemorrhagic complications. They studied 23 cases of polycythemia vera and found no difference in the levels of fibrinogen or degree of fibrinolysis as compared with normal persons. However, they noticed that the fibrin clot formed in patients with polycythemia vera did not satisfactorily hold red cells, thus producing a prominent fallout phenomenon. This suggested a defect in the fibrin itself as a factor in the hemorrhagic phenomenon.

## DISCUSSION

The two cases of polycythemia vera described in this report were of surgical interest because the initial manifestations of the disease were gangrenous changes in the lower extremities. The first case presumably was associated with arteriosclerosis. The increased viscosity and sluggish flow probably compounded the arteriosclerotic obstruction. Following treatment of the polycythemia the skin lesions healed and symptoms disappeared, only to recur years later when the disease was again out of hand. In the second case the diagnosis was obscured by blood loss resulting from a duodenal ulcer which masked the hematologic findings typical of polycythemia. However, a decidedly elevated platelet count led to the diagnosis, which was later verified by marrow studies and subsequent clinical course. Whether the thrombotic lesions resulted from increased viscosity of the blood before the duodenal hemorrhage or from hypercoagulability associated with the high platelet count is not known. In this instance, there was no evidence of arteriosclerosis in the amputated specimen or on arteriography. However, thrombotic complications had previously necessitated the amputation of one leg and a transmetatarsal amputation on the opposite side. It is probable that if the polycythemia had been recognized and treated earlier, major amputation would not have been necessary. With adequate treatment, there has been no further progression of the vascular disease in the extremities.

As roentgenographic techniques have improved, more and more patients are being studied with arteriography. The compiled results of our studies show a large incidence of arteriosclerosis of major vessels which is not associated with symptomatic ischemic extremities. It is our feeling that there may not be a significant difference in atherogenesis between the group of patients with polycythemia vera and a cross-section of population of a similar age group.

It is known that there are significant hemodynamic alterations in polycythemia vera related to viscosity; these are productive of decidedly reduced perfusion rates. In the light of this knowledge, it seems most reasonable to postulate that arteriosclerotic lesions that remain asymptomatic in a patient with a normal blood viscosity and perfusion rate, might very well become significant and symptomatic in a patient with increased viscosity and an already diminished perfusion rate. A moderate extension of these minimal lesions would slow the circulation even more, with a tendency toward earlier thrombosis. Control of the underlying hematologic disease may be sufficient to reverse the symtomatic vascular manifestations in these patients.

Although the diagnosis of polycythemia is usually obvious in the routine blood studies made on patients admitted to hospital, Case 2 emphasized that associated disease, such as bleeding peptic ulcer, may mask the usual elevation of red blood cells. In outpatients, routine blood measurements may not

be made until irreversible peripheral vascular disease has occurred. Thus it seems important to emphasize the peripheral thrombotic manifestations of this disease in order to effect earlier recognition and treatment.

Veterans Administration Hospital, 42nd Avenue and Clement Street, San Francisco 94121 (Blaisdell).

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